Applicant: Judith McInally et al.

Serial No.: To Be Assigned

Filed

Page

: Herewith

3 of 9

Attorney's Docket No.: 06275-455US1 / 100927-1P US 10 / 538452

JC17 Rec'd PCT/PTO 10 JUN 2005

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A compound of formula (I):

$$R^{1} \xrightarrow{\text{Het}} R^{4} \xrightarrow{R^{5}} R^{6}$$

$$N \xrightarrow{I_{2}} R^{3} \xrightarrow{R^{3}} O R^{7} \xrightarrow{R^{8}} R^{8}$$
(I)

 R^1 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R² is independently aryl, heteroaryl or a group C₁₋₆ alkylR⁹, CO(C₁₋₆ alkyl)R⁹ or $SO_2(C_{1-6}alkyl)R^9$; where R^9 is anylor heteroaryl:

or R¹ and R² together with the nitrogen atom to which they are attached form a 4 to 7membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by one or more C₁₋₆ alkyl, amino, hydroxy, CO₂C₁₋₆ alkyl, COC₁₋₆ alkyl, halogen, C₁₋₆ alkylhydroxy, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR¹ group, C₁₋₆ alkylNR¹²R¹³ where R¹² and R¹³ are independently hydrogen or C₁₋₆ alkyl, CONR¹²R¹³, or optionally substituted by C₁₋₆ alkylR⁹, aryl, phenoxy, COaryl, COheteroaryl or a heteroaryl group, the latter six groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR¹²R¹³, SO₂NR¹²R¹³, SO₂R¹², trifluoromethyl, NHSO₂R¹², NHCOR¹², ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C_{1-6} alkyl NR¹⁰R¹¹, SR¹² or NR¹⁰R¹¹:

Serial No.: To Be Assigned

Filed : Herewith Page : 4 of 9

Het is a heteroaryl ring chosen from pyridine, pyrimidine, pyrazine, pyridazine or triazine and optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12} , trifluoromethyl, $NHSO_2R^{12}$, $NHCOR^{12}$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

R³ is independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

 R^4 is independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl C_{1-5} alkyl or heteroaryl C_{1-5} alkyl, the latter three groups being optionally substituted by one or more halogen, amino, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

R⁵ is independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R⁶ is independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;

R⁷ is independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl; and

 R^8 is independently hydrogen, aryl, heteroaryl or C_{1-6} alkyl optionally substituted with one or more aryl, heteroaryl, halogen, amino, hydroxy, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12} , $NHSO_2R^{12}$, $NHCOR^{12}$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$; or a pharmaceutically acceptable salt thereof.

- 2. (Original) A compound according to claim 1 in which R^1 is hydrogen or C_{1-6} alkyl and R^2 is CH_2R^9 or $CH_2CH_2R^9$ where R^9 is phenyl or a 5- or 6-membered aromatic ring containing one or two heteroatoms and optionally substituted by C_{1-6} alkyl.
- 3. (Currently amended) A compound according to claim 1 [[or 2]] in which R¹ and R² together with the nitrogen atom to which they are attached form a piperidine, piperazine, pyrrolidine, morpholine, or thiomorpholine ring optionally substituted by CH₂OH, CH₂CH₂OH, hydroxy, CONH₂, phenyl, phenoxy, or C(O)-furyl, the latter three groups being optionally substituted by halogen, in particular chloro.
- 4. (Currently amended) A compound according to any one of claims 1 to 3 claim 1 in which R^3 is hydrogen.

Serial No.: To Be Assigned

Filed : Herewith Page : 5 of 9

5. (Currently amended) A compound according to any one of claims 1 to 4 claim 1 in which R⁴ is hydrogen.

- 6. (Currently amended) A compound according to any one of claims 1 to 5 claim 1 in which R^5 is hydrogen or phenyl optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy.
 - 7. (Currently amended) A compound of formula (I) selected from:

 $N\sim1\sim-[Cyano(2-methoxyphenyl)methyl]-N\sim2\sim-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide,$

 $N\sim1\sim-[Cyano(2-methoxyphenyl)methyl]-N\sim2\sim-(2-piperazin-1-ylpyrimidin-4-yl)-L-leucinamide,$

N-[Cyano(2-methoxyphenyl)methyl]-N-(2-morpholin-4-ylpyrimidin-4-yl)-L-phenylalaninamide,

 $N\sim1\sim-[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N\sim2\sim-(2-morpholin-4-yl)-L-alaninamide.$

N-[2-(Benzylamino)pyrimidin-4-yl]-N-(cyanomethyl)-L-phenylalaninamide,

 $N-\{2-[Benzyl(methyl)amino] pyrimidin-4-yl\}-N-(cyanomethyl)-L-phenylalanina mide$

N-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide,

 $N\sim2\sim-[2-(Benzylamino)pyrimidin-4-yl]-N\sim1\sim-(cyanomethyl)-3-cyclohexyl-L-alaninamide,$

 $N\sim2\sim-\{2-[Benzyl(methyl)amino]$ pyrimidin-4-yl $\}-N\sim1\sim-(cyanomethyl)-3-cyclohexyl-L-alaninamide,$

 $N\sim2\sim-\{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl\}-N\sim1\sim-(cyanomethyl)-3-cyclohexyl-L-alaninamide,$

N~1~-(Cyanomethyl)-N~2~-(4-morpholin-4-ylpyrimidin-2-yl)-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide,

Serial No.: To Be Assigned

Filed : Herewith Page : 6 of 9

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-[2-(4-hydroxy-4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide,$

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-\{2-[methyl(pyridin-3-ylmethyl)amino]pyrimidin-4-yl\}-L-leucinamide,$

 $N\sim 2\sim {2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N\sim 1\sim {(cyanomethyl)-L-leucinamide,}$

 $N\sim2\sim-\{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl\}-N\sim1\sim-(cyanomethyl)-L-leucinamide,$

 $N\sim2\sim-\{2-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]pyrimidin-4-yl\}-N\sim1\sim-(cyanomethyl)-L-leucinamide,$

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-\{2-[methyl(thien-3-ylmethyl)amino]pyrimidin-4-yl\}-L-leucinamide,$

 $N\sim1\sim$ -(Cyanomethyl)- $N\sim2\sim$ -(2-thiomorpholin-4-ylpyrimidin-4-yl)-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-[2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide,

 $N\sim 1\sim -(Cyanomethyl)-N\sim 2\sim -\{2-[2-(hydroxymethyl)piperidin-1-yl]pyrimidin-4-yl\}-L-leucinamide,$

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-\{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]pyrimidin-4-yl\}-L-leucinamide,$

 $N\sim 1\sim -(Cyanomethyl)-N\sim 2\sim -[2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide,$

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-\{2-[4-(2-furoyl)piperazin-1-yl]pyrimidin-4-yl\}-L-$

 $N\sim2\sim{2-[3-(Aminocarbonyl)piperidin-1-yl]pyrimidin-4-yl}-N\sim1\sim{(cyanomethyl)-L-leucinamide}$

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-\{2-[methyl(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl\}-L-leucinamide,$

 $N\sim2\sim-[2-(4-Benzylpiperidin-1-yl)pyrimidin-4-yl]-N\sim1\sim-(cyanomethyl)-L-leucinamide,$

 $N\sim1\sim-(Cyanomethyl)-N\sim2\sim-[2-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide,$

N~1~-(Cyanomethyl)-N~2~-[2-(4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide,

Serial No. : To Be Assigned

Filed : Herewith Page : 7 of 9

 $N\sim 1\sim -(Cyanomethyl)-N\sim 2\sim -\{2-[4-(2-hydroxyethyl)piperidin-1-yl]pyrimidin-4-yl\}-L-leucinamide,$

 $N\sim2\sim-\{2-[4-(3-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl\}-N\sim1\sim-(cyanomethyl)-L-leucinamide,$

N~1~-(Cyanomethyl)-N~2~-[2-(4-phenoxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-[2-(3-phenylpyrrolidin-1-yl)pyrimidin-4-yl]-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-(2-{methyl[(3-methylisoxazol-5-yl)methyl]amino} pyrimidin-4-yl)-L-leucinamide,

and pharmaceutically acceptable salts thereof.

8. (Canceled)

- 9. (Currently amended) A pharmaceutical composition which comprises a compound of the formula (I) as defined in any one of claims 1 to 7 claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.
- 10. (Currently amended) A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound of the present invention as defined in any one of claims 1 to 7 claim 1 or a pharmaceutically acceptable salt thereof.
- 11. (Currently amended) A method for treating pain, such as neuropathic pain, in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound as defined in any one of claims 1 to 7 claim 1, or a pharmaceutically acceptable salt thereof.

Serial No.: To Be Assigned

Filed: Herewith Page: 8 of 9

12. (New) A pharmaceutical composition which comprises a compound according to claim 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

- 13. (New) A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound according to claim 7 or a pharmaceutically acceptable salt thereof.
- 14. (New) A method for treating pain, such as neuropathic pain, in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound according to claim 7, or a pharmaceutically acceptable salt thereof.
 - 15. (New) A compound according to claim 2 in which R³ is hydrogen.
 - 16. (New) A compound according to claim 2 in which R⁴ is hydrogen.
- 17. (New) A compound according to claim 2 in which R^5 is hydrogen or phenyl optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy.
 - 18. (New) A compound according to claim 3 in which R³ is hydrogen.
 - 19. (New) A compound according to claim 3 in which R⁴ is hydrogen.
- 20. (New) A compound according to claim 3 in which R^5 is hydrogen or phenyl optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy.